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UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
08/794,851	02/04/97	BARANY	F	19603/461(CR

HM22/0608

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EXAMINER	
RICIGLIANO, J	
ART UNIT	**PAPER NUMBER**
1618	21

DATE MAILED: 06/08/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/794,851	Applicant(s) Barany et al.
	Examiner Joseph W. Ricigliano Ph. D.	Group Art Unit 1618

☒ Responsive to communication(s) filed on *Mar 1, 1999*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-88 and 137-148* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-88 and 137-148* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

KEITH D. MacMILLAN
PRIMARY EXAMINER

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Please Note: The examiner's art unit designation has changed to 1618.

Continued Prosecution Application

1. The request filed on 3/1/99 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/794,851 is acceptable and a CPA has been established. An action on the CPA follows.

DETAILED ACTION

2. This action is responsive to the amendment of 3/1/99 (paper number 20).

3.Claims 1-147 were previously pending in the instant application. Claims 89-137 have been canceled, and new claim 148 added by the amendment of 3/1/99

4. Claims 1-88 and 138-148 are pending in the instant application. Claims 67-74 withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 1-88 and 138-147 are currently being examined on the merits.

Rejections Withdrawn

The following rejections have been withdrawn:

5. Claims 1-5, 11-21 and 24-43, 45-66, 75-77,79, 80, 83, 87, 88 and 138-147 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiedmann et al (1994) in view of, Barany (PCR Methods and Applications, 1991a) Zaun et al (US 5, 415, 839) and Guo et al (1994)/

6. Claims 6-10, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiedmann et al (1994) in view of, Barany (PCR Methods and Applications, 1991a) Zaun et al

(US 5, 415, 839) and Guo et al (1994)as applied to claims 1-5, 11-21 and 24-43, 45-66, 75-77,79, 80, 83, 87, 88 and 138-147 *supra* in further view Telenti et al.

7. Claim 44 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wiedmann et al (1994) in view of, Barany (PCR Methods and Applications, 1991a) Zaun et al (US 5, 415, 839) and Guo et al (1994) as applied to claims 1-5, 11-21 and 24-43, 45-66, 75-77,79, 80, 83, 87, 88 and 138-147.

8. Claims 78, 82, 84-86 are rejected under 35 U.S.C. 103(a) as being unpatentable Wiedmann et al (1994) in view of, Barany (PCR Methods and Applications, 1991a) Zaun et al (US 5, 415, 839) and Guo et al (1994) as applied to claims 1-5, 11-21 and 24-43, 45-66, 75-77,79, 80, 83, 87, 88 under 35 U.S.C. 103(a) supra in further view of Sambrook et al.

9. These rejections were withdrawn in view of applicants' amendment to limit the first oligo nucleotide probes to those having an oligonucleotide addressable array specific portion. As the Zaun reference which was cited for the use of probes with a capture portion (and arrays which capture them) does not teach the use of probes having oligonucleotide capture portions the rejections of record are overcome.

10. The rejection of claims 12, 16, 18, 19, 20, 22, 26, 30 and 34 as being indefinite for the recitation that the "nucleotides positions which require overlapping oligonucleotide probe sets." This vague and indefinite because it is unclear when positions require overlapping probe sets has also been withdrawn. The rejection is withdrawn in view of applicants' arguments that it is clear they are referring to nucleotide positions that are prioximate (i.e., would be close enough to interfere with a second probe set binding and ligating effectively).

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-88 and 137-148 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use o f second oligonucleotide probes which have an oligonucleotide target specific portion, does not reasonably provide enablement for a non-oligonucleotide target specific portion. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-88 and 138-147 are directed toward a method of identifying a plurality of sequences. The disclosure teaches the identification of nucleotide sequences using oligonucleotide probes having oligonucleotide target sequences. However, the detection of nucleotide sequences using probes with non-nucleotide target specific portions does not appear to be within the scope of reasonable experimentation. The factors to be considered in a determination of undue experimentation are disclosed in *In re Wands,* (U.S.P.Q. 2d 1400 (CAFC 1988). The factors to be considered include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the predictability of the art and the breadth of the claims.

A number of factors would prevent one of skill in the art from practicing the invention without undue experimentation, these are summarized as follows:

1) The specification fails to give adequate direction and guidance in the use of probes which are not nucleic acids for the detection of target sequences which nucleotide sequences.

2) Applicants have failed to provide any working examples of the detection of sequences using probes that do not have oligonucleotide target sequences.

3) The breadth of the claims encompass oligonucleotide probes a target specific portion which are not limited to oligonucleotides.

4) The state of the prior art is such that the ligation reactions which are required for the instant method can only be conducted by ligating nucleotides.

5) The art is inherently unpredictable because it is not clear how to predict a priori which can be ligated by a ligase-mediated reaction.

Therefore, while it is true that the level of skill in the art is high, it would require undue experimentation to use the invention commensurate in scope with that claimed in the absence of explicit guidance by applicants as to what types of probes other than those with oligonucleotide target specific portions can be utilized as set forth above.

Applicants may wish to consider amending the claims to recite that target specific sequences are oligonucleotides. For example such limitations may be considered in respect to the second probe in claim 1 and the probes of claim 7 etc.

13. Claims 58-60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the detection of sequences which are clearly known, does not reasonably provide enablement for the use of the instant method to detect sequences involved in genetic disorders in which the sequences involved are not clearly established. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to utilize the invention commensurate in scope with these claims.

Claims 58-60 are directed toward methods of using Ligase Detection assays to detect genetic disorders. The disclosure teaches how to detect sequences which may have specific changes. However, detection of genetic lesions which have not been specifically mapped to sequenced sites in the genome does not appear to be within the scope of reasonable experimentation. The factors to be considered in a determination of undue experimentation are disclosed in *In re Wands,* (U.S.P.Q. 2d 1400 (CAFC 1988). The factors to be considered include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the predictability of the art and the breadth of the claims.

Contrary to applicants claims a number of factors would prevent one of skill in the art from practicing the invention without undue experimentation, these are summarized as follows: 1) The specification fails to give adequate direction and guidance as to the use of the instant ligase detection reactions which require specific knowledge of the sequence to design primers which the target sequences are not explicitly known in detail.

2) Applicants have failed to provide any working examples of means by which targets could be identified using the instant methods.

3) The breadth of the claims encompasses virtually any genetic disorder due to changes in the genomic nucleic acids in any species.

4) The state of the prior art is such that it may take years of analysis to identify a genetic locus involved in a disorder, more time to obtain and sequence the specific site and determine the specific changes correlating with a disease state prior to the construction of probes for conducting the claimed detecting method.

5) The art is inherently unpredictable because the analysis of diseases which have a genetic basis can be influenced by many parameters making it difficult to clearly determine even a simple pedigree analysis to establish that the disease is genetically transmitted. Moreover, the subsequent direct isolation of the sequence involved including the specific nucleotide changes may be difficult to establish in view of the fact that compensatory mutations may occur at sites far removed from the loci which are thought to be involved.

Therefore, while it is true that the level of skill in the art is high, it would require undue experimentation to use the invention commensurate in scope with that claimed in the absence of specific knowledge of the sequences involved in detecting such literally any genetically liked disorder in any species as set forth above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 1-88 and 138-147 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-88 and 138-147 have been amended to recite: "a first oligonucleotide probe having an oligonucleotide target-specific portion and an oligonucleotide addressable array-specific portion, wherein the oligonucleotide addressable array specific portion is separate and distinct from the oligonucleotide-target specific portion" This is vague and indefinite because it is unclear if the probe is comprised one probe with distinct elements or two separate and distinct sequences (i.e., separate nucleotides somehow vaguely linked). Therefore, it is not possible to determine the metes and bounds of the invention as claimed.

Applicants may wish to consider the following language with respect to the first probes

"a first oligonucleotide probe having an oligonucleotide target-specific portion and an oligonucleotide addressable array-specific portion, wherein the oligonucleotide addressable array specific portion is comprised of an oligo nucleotide sequence that is distinct from the oligonucleotide sequence of the target specific portion." Applicants are reminded to indicate where support can be found in the specification for this or any amendment.

15. Claim 13 recites "similar" hybridization conditions. This is vague and indefinite as it is unclear what limitations apply to "similar" and hence it is not possible to determine the metes and bounds of the invention as claimed. If applicants intend this to mean the probes set can be

successfully ligated in the presence of their target sequences under a single set of LDR conditions then applicants should amend the claims to specifically recite this.

16. Claim 44 recites "for a particular oligonucleotide probe set. This is vague and indefinite because it is unclear which oligonucleotide probe set applicants are referring to as there are a plurality of oligonucleotide probe set forth in claim 1 from which claim 44 depends. Moreover, there is no antecedent basis in the subjecting step or in the any other part of claim 1 to set forth a particular oligonucleotide set. Therefore, it is not possible to determine the metes and bounds of the invention as claimed.

17. Claim 81 recites the limitation each capture oligonucleotide differs from its adjacent capture oligonucleotide on the array by at least one out of ever four of the nucleotides when the nucleotides are aligned at one end. This is vague and indefinite because it is unclear if applicants are intending to compare the sequence or the composition of the oligonucleotides. Moreover, it is unclear how to compare oligonucleotides that different in length or which end of the oligonucleotides is being compared.

18. Claims 67-74 recite the solid support is functionalized with olefin amino hydroxyl . . . functionalities. This is vague and indefinite because it is unclear if these are intended to be functionalities which are subsequently used to attach nucleotides or functionalities which are introduced after nucleotides are attached, or functionalities introduced for some other reason. Therefore, it is not possible to determine the metes and bounds of the invention as claimed.

Conclusion

19. The prior art made of record and not relied upon is considered pertinent to applicants' disclosure.

20. Shuber 5,834,181 teaches the use of ligase mediated reactions in the detection of target nucleotide sequences. Shuber however does not specifically recite the use of probe sets having oligonucleotides which are specific for an array of target nucleotides.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph W. Ricigliano Ph. D. whose telephone number is (703) 308-9346. The examiner can be reached on Monday through Thursday from 7:00 A.M. to 5:30 P.M.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist whose telephone number is (703) 308-0196.

22. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Donald E. Adams Ph. D., can be reached at (703) 308-0570.

Joseph W. Ricigliano Ph. D.

KEITH D. MacMILLAN
PRIMARY EXAMINER